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Fat on the brain

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The study by Borg and colleagues featured in this issue of *The Journal of Physiology* suggests that a high fat diet could quite literally leave you with 'fat on the brain' (Borg *et al.* 2012). According to this research, an excess intake of dietary fat translates into increased lipid content of brain tissues, which is likely to have significant (and probably negative) consequences for brain function.

This work builds on previous studies in both animals and humans which have shown that consuming excessive amounts of fat in the diet leads to an increased accumulation of lipid in peripheral tissues which aren't designed for fat storage, particularly the skeletal muscle and liver, in a process referred to as ectopic fat storage (Frayn, 2001; Kopecky *et al.* 2002). The resulting increase in the fat content of these tissues interferes with their ability to function normally, and is implicated in many of the co-morbidities associated with diet-induced obesity, in particular insulin resistance (Kopecky *et al.* 2002; Ravussin & Smith, 2002). In the skeletal muscle and liver, for example, increases in lipids such as ceramide and diacylglycerol block insulin signalling, leading to reduced glucose uptake in the muscle and impaired suppression of glucose output by the liver, both of which contribute to peripheral hyperglycaemia and ultimately lead to whole body insulin resistance (Kopecky *et al.* 2002). Whilst the association between high fat diets and increased fat accumulation is well established and has been looked at in a range of important metabolic tissues, including the pancreas, liver and muscle, the study by Borg and colleagues is the first to show that this also occurs in the brain.

In this study, mice were fed for 12 weeks on either a low fat diet, which supplied 5% energy from fat, or a micronutrient-matched high fat diet, supplying 59% energy from fat. The hypothalami (a region known to be critical for the regulation of energy balance) of the mice were then collected and examined for signs of lipid accumulation. These investigations revealed that the levels of several lipids, particularly those known to be involved in insulin resistance, were significantly elevated in the brains of the mice on the high fat diet at the end of the feeding period. Importantly, further studies showed that the accumulation of lipid in the brains of these mice was specifically related to consumption of a high fat diet and not obesity *per se*, since genetically obese leptin-deficient mice consuming a low fat diet didn't show increased brain lipid levels, despite being of a similar body weight to the diet-induced obese mice. It will be interesting in future studies to determine what happens to brain lipid levels in animals who are resistant to diet-induced obesity, since the results of the Borg paper suggest that even if these animals remain lean, they could still exhibit significant lipid accumulation in the brain and the associated adverse consequences in the long term.

The other question addressed in this paper is the all-important one of reversibility. In previous studies, exercise has proved to be an effective approach for promoting fat oxidation, reducing triglyceride content in skeletal muscle and improving peripheral insulin sensitivity (Snel *et al.* 2012). Based on this, it might be expected that placing high-fat-fed mice on an exercise regimen might help to reverse the accumulation of brain lipids. However, the results of this paper clearly showed that even when mice consuming a high-fat diet were placed on a fairly substantial programme of treadmill running for 6 weeks, brain lipid content was not significantly different from high-fat-fed mice who were sedentary. This was despite positive effects of the exercise intervention on fitness (running capacity), fasting glucose levels and glucose tolerance. So, whilst it might be possible to overcome some of the negative effects of a high fat diet by exercise, it would appear that the only way to reduce brain lipid levels is by reducing the intake of fat in the diet.

This paper clearly shows that consuming a high fat diet can literally result in fat on (or rather in) the brain. Knowing what we do about the negative effects of increased lipid accumulation on the function of other tissues, it seems highly likely that accumulation of excess lipid in brain tissues will have negative effects on the many crucial regulatory systems of the brain. Following on from these findings, it will be important to move towards determining the full impact of lipid accumulation on brain function and investigating potential strategies for preventing and reversing this process.

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